REMARKS

Claims 16-23 and 25-28 are pending.

The Amendments

Claim 16 is amended to change "gamma" to "γ" for consistency.

Claim 22 is amended to delete "selected."

No new matter is introduced in any of the amendments.

The Response

35 U.S.C. §103(a) Rejections

1. Claims 16-23 and 25-28 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Huland in view of both Debs and Ruskewicz, and further evidenced by Nayar or Hora. Claim 24 is canceled. The rejection is traversed.

Claim 22 recites an aerosol formulation wherein the aerosol particles are within a defined size range of (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns, and the biological activity and protein molecular size of interferon gamma are substantially the same as those of the aqueous solution. The cited references, either alone or in combination, do not teach or suggest any of the above claimed features, let alone the combined claimed features.

The cited references do not teach or suggest claimed particle size ranges

None of Huland, Debs, Nayar, and Hora disclose a composition of γ-IFN having the claimed defined particle size range.

At Column 17, lines 58-60, Ruskewicz discloses "an aerosol preferably having a particle size in the range of about 1 to 12 microns, more preferably of about 3.0 to 6.0 microns." However, Ruskewicz does not teach or suggest the claimed particle size range of: (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns. Each of the claimed particle size ranges has a unique application. For example, Applicants have described the desired droplet particle size of less than 1 micron for treating cystic fibrosis, 1-3

microns for delivery to bronchial sites, and 3-5 microns for administering systemically (see application at page 15, lines 1-7).

The Examiner states that the fact that Ruskewicz teaches "about" the claimed 3-5 microns could be considered as "about 3-6 microns." Applicants respectfully disagree. **Claim 22 does not recite "about" 3-5 microns, but specifically recite (iii) 3-5 microns, (iv) 5-10 microns, and other sizes.** Ruskewicz does not teach or suggest any of the claimed size range. The Examiner uses hindsight to arbitrarily change the 6 micron size described in Ruskewicz to 5.4 micron, then round off 5.4 micron to 5 micron in order to produce the claimed 5 micron value. A skilled person would not interpret the referenced 3-6 microns as being the same as the claimed 3-5 microns, particularly in view of the fact that Claim 22 has specified 3-5 microns and 5-10 microns as different size ranges.

Neither of the cited references teaches or suggests the claimed particle size ranges, therefore, the combination of the cited references does not produce the claimed defined particle size ranges.

<u>The cited references do not teach or suggest claimed retention of substantially the same biologic activity</u>

Claim 22 recites a composition of aerosol droplet particles with an interferon- γ biological activity and molecular size distribution substantially the same as those of the aqueous interferon gamma solution. In the application at page 13, lines 10-17, Applicants describe that:

> In addition to predictability and uniformity in droplet size, it is important that the aerosolization process, which is associated with high local shear forces, does not significantly alter the biological activity or the molecular size distribution of γ-IFN in the aerosol. The two characteristics may be linked, inasmuch as γ -IFN is active in a dimerized state, and may be expected to lose activity, either by monomerization of aggregation, when subjected to the high shear forces associated with aerosolization, and/or by protein denaturation at the liquid/air interfaces in small aerosol droplets.

None of the cited references Huland, Debs, Ruskewicz, Nayar or Hora describe an aerosol droplet composition of γ-IFN with retention of substantially similar γ-IFN activity compared with the liquid composition prior to aerosolization. Huland, Ruskewicz, Nayar or Hora does not measure the biologic activity of IFN- γ. Debs merely describes the immunomodulatory effects of aerosolized rMuIFN- γ on rat alveolar macrophage and blood

monocyte function. Debs does not measure the IFN- γ biological activity before and after aerosolization. The mere presence of some stimulatory potency in an aerosolized composition does not mean that substantially the same γ-IFN biological activity remains in the aerosol droplets as compared with the formulation prior to aerosolization. The biologically active form of γ-IFN is made up of two monomers held together by a non-covalent bond. **It is known in the art that shear forces and other physico-chemical challenges- such as those encountered during an attempt to aerosolize a liquid γ-IFN solution- are not well tolerated by the molecule** (see Declaration of Peter Van Vlassalaer, filed February 17, 2004). It is important for a therapeutic product to retain substantially the same γ-IFN activity in the aerosol droplets such that potent γ-IFN can be delivered to a patient to achieve a therapeutic effect.

The Examiner also asserts that full biological activity of rHuTNF-α was retained in a condensate after aerosolization in Debs. However, rHuTNF-α and γ-IFN are structurally and chemically distinct proteins. **The ability to aerosolize one protein (rHuTNF-α) without loss of its activity does not indicate the ability to aerosolize another protein (γ-IFN), which tends to monomerization or aggregation, without loss of γ-IFN activity.** Based on Debs' teaching, a skilled person would not derive the conclusion that γ-IFN can retains full biological activity after aerosolization.

On the contrary, Applicants have demonstrated in Figure 6 that three aerosolized formulations prepared by Applicants showed substantially the same biological activity as that of the non-aerosolized solution (see Figure 6 and page 13, line 31 through page 14, line 4).

<u>The cited references do not teach or suggest claimed retention of substantially the same molecular size distribution</u>

None of the cited references Huland, Debs, Ruskewicz, Nayar or Hora describe a composition of γ-IFN with substantially the same molecular size distribution after aerosolization. None of the cited references disclose a molecular size distribution. The limitation of **substantially the same molecular size distribution in Claim 22 refers to protein size at a molecular level, not droplet particle sizes. It is important to maintain the biologically-active dimer form of γ-IFN after aerosolization.**

The Examiner argues that Ruskewicz teaches retention of substantially the same γ-IFN molecular size distribution. However, Ruskewicz only disclose aerosol particle size, but not protein molecular size.

On the contrary, Applicants have demonstrated in Figures 7 and 8 that by protein molecular analysis of the collected aerosol samples, aerosolization of IFN- γ solution has no measurable effect on the molecular size distribution, i.e., the state of dimerization, monomerization or aggregation of the IFN- γ (see Figures 7 and 8 and page 14, lines 21-25).

The Examiner states that one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. Applicants assert that none of the cited references have taught or suggested any of the claimed features as stated above, therefore the combination of the references do not render Claims 16-23 and 25-28 obvious.

2. Claims 16-23 and 25-28 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Huland and Jaffe in view of both Debs and Ruskewicz as further evidenced by Nayar or Hora.

As discussed above, Huland, Debs, Ruskewicz, Nayar, and Hora do not render Claims 16-23 and 25-28 obvious. The addition of Jaffe does not cure the deficiency of other references.

Jaffe describes a formulation with a particle size of "0.1-3 μm mass median diameter (50% of droplets less than or equal to 0.1-3 μm)" (see page 297, right column, first full paragraph). Jaffe does not teach or suggest the claimed particle size of: (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns.

Although Jaffe discloses that IFN-γ can be aerosolized and inhaled while retaining some biologic activity after reaching the lower respiratory tract, Jaffe does not show that the biological activity of the aerosolized γ-IFN is substantially the same as that of the aqueous γ-IFN solution. Further, Jaffe does not show that the molecular size distribution of the aerosolized γ-IFN is substantially the same as that of the aqueous γ-IFN solution.

Accordingly, the 35 U.S.C. 103(a) rejection of Claims 16-23 and 25-28 over Huland and Jaffe in view of Debs, Ruskewicz, Nayar and Hora should be withdrawn.

35 U.S.C. §112, Second Paragraph Rejection

Claims 16-23 and 25-28 are rejected under 35 USC 112, second paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The rejection is traversed in parts and overcome in parts in view of the claim amendment.

The Examiner contends that Claim 22 recites the term "selected γ-IFN biological activity" without specifying which biological activity of γ-IFN is selected. Applicants have amended Claim 22 to delete "selected."

The Examiner also contends that the terms "biological activity substantially the same" and "molecular size distribution substantially the same" are vague and indefinite. Applicants do not agree.

The court held that the limitation "to substantially increase the efficiency of the compound as a copper extractant" was definite in view of the general guidelines contained in the specification. In re Mattison, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The court held that the limitation "which produces substantially equal E and H plane illumination patterns" was definite because one of ordinary skill in the art would know what was meant by "substantially equal." Andrew Corp. v. Gabriel Electronics, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988).

Here, Applicants have demonstrated the retention of γ-IFN biological activity and γ-IFN molecular size distribution. In view of the general guidelines contained in the specification, a skilled person would know what is meant by ""substantially the same" as that of the aqueous γ-IFN solution in Claim 22.

Therefore, the 112, second paragraph rejection of Claims 16-23 and 25-28 should be withdrawn.

CONCLUSION

Applicants believe that the application is now in good and proper condition for allowance. Early notification of allowance is earnestly solicited. The Examiner is invited to contact Applicants' representative at the number below.

Respectfully submitted,

Date: April 19, 2006

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